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ORIGINAL RESEARCH ARTICLE

Elderly Patients with Diabetes Experience a Lower Rate of Nocturnal Hypoglycaemia with Insulin Degludec than with Insulin Glargine: A Meta-Analysis of Phase IIIa Trials

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Abstract

Background and Objective Elderly patients with diabetes are more vulnerable to the occurrence and effects of hypoglycaemia; therefore, treatments with low risk of hypoglycaemia are preferred in this population. This study aimed to compare hypoglycaemia rates between insulin degludec (IDeg) and insulin glargine (IGlar) in elderly patients.

Methods Hypoglycaemia data from patients ≥ 65 years of age with type 1 (T1DM) or type 2 (T2DM) diabetes from seven randomised, treat-to-target phase IIIa trials were used to compare IDeg and IGlar in a pre-planned meta-analysis. Overall, 917/4345 (21 %) randomised patients in the seven trials were elderly (634 IDeg, 283 IGlar). Overall confirmed hypoglycaemia was defined as <3.1 mmol/L or severe hypoglycaemia (symptoms requiring external

assistance). Nocturnal hypoglycaemia included confirmed episodes from 0001 to 0559 hours (inclusive). Treatment comparisons of hypoglycaemia in T1DM patients were not performed due to low numbers of elderly patients with T1DM randomised (43 IDeg, 18 IGlar); statistical comparisons were also not made for severe hypoglycaemia due to the low number of events.

Results In elderly patients with T2DM, the rate of overall confirmed hypoglycaemia was significantly lower with IDeg than IGlar [estimated rate ratio (ERR) 0.76 (0.61; 0.95)_{95 % CI}]; nocturnal confirmed hypoglycaemia was also significantly lower with IDeg [ERR 0.64 (0.43; 0.95)_{95 % CI}]. Confirmed hypoglycaemia occurred in the majority of T1DM patients, whereas severe episodes occurred infrequently and at similar rates in both treatment groups in T1DM and T2DM.

Conclusion Results of this pre-planned meta-analysis in elderly patients with diabetes demonstrate a significant reduction in hypoglycaemic events with IDeg relative to IGlar.

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1 Introduction

The prevalence of diabetes in the elderly is high; current estimates indicate that in the US, 26.9 % of people ≥ 65 years of age are diagnosed with the condition [1]. As the US population ages and the rates of individuals who are overweight or obese continue to rise, both the prevalence and burden of diabetes in the elderly is expected to increase substantially over the next several decades [2].

The American Diabetes Association (ADA) recommends that glycaemic goals for elderly patients with diabetes should be individualised, based on the presence or absence of cognitive impairment, functional impairment,

major comorbidities and limited life expectancy [3–5]. Medical management of elderly patients with diabetes is challenging due to a number of factors [6–8]. For example, elderly patients are more likely to have diabetes that is complicated by end-organ damage and, in general, long duration of disease is associated with defective glucose counter-regulation leading to increased risk of hypoglycaemia and hypoglycaemia unawareness.

Episodes of severe hypoglycaemia in the elderly have been associated with increased risk of cardiac autonomic dysfunction [9], falls [10, 11], and dementia [12]. Moreover, elderly patients often live alone, which may make the consequences of hypoglycaemia and hypoglycaemic unawareness even more detrimental. For these reasons, a 2012 joint position statement by the ADA and the European Association for the Study of Diabetes (EASD) stated that, in this at-risk population, drug selection should favour agents that minimise the risk of hypoglycaemia [4].

Insulin therapy is required to achieve glycaemic control in all patients with type 1 diabetes (T1DM) and in many patients with type 2 diabetes (T2DM) who are not adequately controlled with oral antidiabetic drugs (OADs) or glucagon-like peptide-1 (GLP-1) receptor agonists. While insulin is effective for all patients with diabetes, hypoglycaemia and fear of hypoglycaemia associated with insulin have resulted in delays in both initiation and intensification, thus limiting patients' well-being and their ability to reach glycaemic targets [13].

Insulin degludec (IDeg) is a new basal insulin with an ultra-long duration of action that, upon injection into subcutaneous tissue, forms a depot of soluble multi-hexamers from which insulin monomers are slowly and continuously absorbed into the circulation [14, 15]. In line with clinical pharmacology findings [16–18], IDeg improved glycaemic control with HbA_{1c} reductions that were non-inferior to insulin glargine (IGlar), but with a significantly lower rate of nocturnal hypoglycaemia in the three 1-year phase III trials in T1DM and T2DM [19–21].

A prospective, pre-planned meta-analysis of pooled patient-level data from all seven IDeg phase III trials with IGlar as the comparator confirmed the hypoglycaemia results of the individual trials [22]. The objective of this pre-planned meta-analysis was to compare rates of hypoglycaemia between IDeg and IGlar, specifically in elderly patients ≥ 65 years of age.

2 Methods

2.1 Design of Trials Included in the Meta-analysis

The IDeg phase III clinical development programme (BEGIN) included seven randomised, open-label, treat-to-

target trials of either 26 or 52 weeks' duration comparing once-daily IDeg to once-daily IGlar [19–21, 23–26]. Table 1 summarises the design features of each trial. Two trials (Trials 3583 and 3770) enrolled patients with T1DM and five (Trials 3582, 3668, 3672, 3579 and 3586) enrolled patients with T2DM.

All seven trials enrolled patients who were at least 18 years of age (20 years in Japan), with no upper age limit; data from elderly patients ≥ 65 years of age were included in this meta-analysis. The definition of elderly patients as those who were ≥ 65 years of age was chosen to remain consistent with US FDA guidance [27]. Relevant to this analysis of hypoglycaemia, hypoglycaemic unawareness, or recurrent hypoglycaemia defined as more than one severe hypoglycaemic episode in the last year, were exclusion criteria in the seven clinical trials. Moreover, hypoglycaemic episodes that occurred during the treatment period and posed a safety concern in the opinion of the investigator were criteria for withdrawal. In addition, patients with serious comorbidities were excluded.

Two trials (T1DM Trial 3770 and T2DM Trial 3668) included an additional dosing arm, in which the extremes of once-daily dosing of IDeg were tested by alternating morning and evening dosing from day to day [23, 24]. It was prespecified that data from elderly patients randomised to this enforced and atypical flexible dosing regimen were not included in the meta-analysis because this type of regimen does not reflect the intended use of IDeg in clinical practice.

The primary objective of all seven trials, to demonstrate non-inferiority of IDeg to IGlar with respect to reduction in HbA_{1c} [19–21, 23–26], was achieved by titrating both IDeg and IGlar for each individual patient to reach a pre-breakfast plasma glucose target of <5 mmol/L (<90 mg/dL) using the T1DM and T2DM algorithms of the IDeg programme (algorithm details are available in individual trial publications). HbA_{1c} non-inferiority was a prerequisite to compare the key secondary endpoint of hypoglycaemia [28]. Adherence to the titration algorithm was monitored by a titration committee blinded to treatment.

The seven trials included in this meta-analysis were conducted in accordance with the Declaration of Helsinki [29] and Good Clinical Practice [30]. Protocols were approved by independent ethics committees/institutional review boards prior to the trials, and patients signed informed consent. Trials were conducted between September 2009 and December 2010, and are registered with ClinicalTrials.gov with the following numbers: NCT00982228 (Trial 3583), NCT01079234 (Trial 3770), NCT00972283 (Trial 3582), NCT01006291 (Trial 3668), NCT00982644 (Trial 3579), NCT01068665 (Trial 3672) and NCT01059799 (Trial 3586).

Table 1 Summary of trials included in the meta-analysis [19–21, 23–26]

Trial (duration)	Diabetes population	Elderly patients randomised/all patients randomised (%)	Trial treatment	Randomisation	HbA _{1c} (%; baseline/end of trial)	Reference to primary results
Trial 3583: BEGIN: BB T1 (52 weeks)	Insulin treated, T1DM	39/629 (6)	IDeg OD or IGlar OD + IAsp	3:1	IDeg OD: (7.7/7.3) IGlar OD: (7.7/7.3)	Heller et al. [19]
Trial 3770: BEGIN: FLEX T1 ^a (26 weeks)	Insulin treated, T1DM	22/329 (7)	IDeg OD Flexible, IDeg OD Fixed or IGlar OD, all + IAsp	1:1:1	IDeg OD Fixed: (7.7/7.3) IGlar OD: (7.7/7.1)	Mathieu et al. [23]
Trial 3582: BEGIN: BB T2 (52 weeks)	Insulin treated, T2DM	270/1006 (27)	IDeg OD or IGlar OD + IAsp ± met ± pio	3:1	IDeg OD: (8.3/7.1) IGlar OD: (8.4/7.1)	Garber et al. [20]
Trial 3668: BEGIN: FLEX ^a (26 weeks)	Insulin naïve and insulin treated, T2DM	78/456 (17)	IDeg OD Flexible, IDeg OD Fixed or IGlar OD ± OAD(s)	1:1:1	IDeg OD Fixed: (8.4/7.3) IGlar OD: (8.4/7.1)	Meneghini et al. [24]
Trial 3579: BEGIN: ONCE LONG (52 weeks)	Insulin naïve, T2DM	292/1030 (28)	IDeg OD or IGlar OD + met ± DPP-4I	3:1	IDeg OD: (8.2/7.1) IGlar OD: (8.2/7.0)	Zinman et al. [21]
Trial 3672: BEGIN: LOW VOLUME (26 weeks)	Insulin naïve, T2DM	94/460 (20)	IDeg OD or IGlar OD + met ± DPP-4I	1:1	IDeg OD: (8.3/7.0) IGlar OD: (8.2/6.9)	Gough et al. [25]
Trial 3586: BEGIN: ONCE ASIA (26 weeks)	Insulin naïve, T2DM	122/435 (28)	IDeg OD or IGlar OD + OAD(s)	2:1	IDeg OD: (8.4/7.2) IGlar OD: (8.5/7.1)	Onishi et al. [26]

BB basal–bolus, DPP-4I dipeptidyl peptidase-4 inhibitor, HbA_{1c} glycosylated haemoglobin, IDeg insulin degludec, IGlar insulin glargine, IAsp insulin aspart, met metformin, OAD oral antidiabetes drug, OD once daily, pio pioglitazone, T1DM type 1 diabetes mellitus, T2DM type 2 diabetes mellitus

^a Patients from the flexible dosing arm were not included in the analysis

2.2 Reporting and Classification of Hypoglycaemic Episodes

Hypoglycaemic episodes were reported by patients either as the result of routine blood glucose monitoring or recognised symptoms. Patients performed routine blood glucose tests using glucose meters calibrated to give plasma glucose results on 3 consecutive days before visits (daily in Trial 3770) and recorded the values in patient diaries. Patients tested their glucose either before and 90 minutes after meals, as well as at bedtime and in the middle of the night (9-point profile), or before meals and at bedtime (4-point profile) multiple times during the trials. In addition, patients were instructed to self-measure their blood glucose with their trial-supplied glucose meter

whenever they experienced symptoms of hypoglycaemia. Patients' self-reported information related to episodes of hypoglycaemia in their diaries, which included date and time of the hypoglycaemic episode, the presence or absence of symptoms, and if the episode was self-treated.

Hypoglycaemic episodes were classified as severe, confirmed or nocturnal confirmed. Severe episodes required assistance from another person to administer carbohydrates or glucagon and did not necessarily have an associated blood glucose measurement. Confirmed hypoglycaemic episodes were either severe episodes or those episodes that had an associated self-measured blood glucose measurement of <3.1 mmol/L (<56 mg/dL), regardless of the presence of hypoglycaemic symptoms. Nocturnal confirmed hypoglycaemic episodes were any

confirmed episodes that occurred from 0001 to 0559 hours (both inclusive). Treatment-emergent episodes of hypoglycaemia were any episodes that occurred from the first dose of trial drug up until 7 days after the last dose of trial drug (i.e. the last trial visit).

2.3 Statistical Methodology

The number and percentage of patients with one or more hypoglycaemic episode, the number of hypoglycaemic episodes in total, and the rate of hypoglycaemia [number of episodes per patient-year of exposure (PYE)] were summarised descriptively by treatment and by population (T1DM, T2DM) for the various hypoglycaemia classifications (severe, overall confirmed and nocturnal confirmed). Descriptive statistics of hypoglycaemia were presented for all patients exposed to treatment [i.e. the safety analysis set (SAS)].

Statistical methodology for the hypoglycaemia meta-analysis of elderly patients was identical to the primary meta-analysis, previously described by Ratner et al. [22], except that only patients ≥ 65 years of age at screening were included in the analysis. The number of treatment-emergent hypoglycaemic episodes was counted for each subject and divided by exposure time, then analysed using a negative binomial regression model adjusted for differences across trials, sex, geographical region, diabetes type, antidiabetic therapy at screening and age. Hypoglycaemic rates are expressed as the number of episodes per PYE. Data from elderly patients in the full analysis set (FAS; consisting of randomised patients) were analysed, and treatment differences presented as estimated rate ratios (ERRs) [IDeg/IGlar] with 95 % confidence intervals (CIs).

Comparisons of the rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were made for elderly subjects in the T2DM trials and the pooled T1DM and T2DM trials. A separate statistical analysis of hypoglycaemia in T1DM was not performed due to the small number of elderly subjects in the two T1DM trials (Table 1). Likewise, no statistical treatment comparisons of severe hypoglycaemia were made because there were very few episodes classified as severe in the elderly population.

The analyses of hypoglycaemia described above included treatment-emergent hypoglycaemic episodes that occurred during the entire trial period (total treatment period), as specified for each trial in Table 1. In addition, separate analyses of treatment-emergent hypoglycaemic events that occurred during the maintenance period (week 16 to the end of the trials) were conducted. The maintenance period was included in order to show results after stable glycaemic control and a stable insulin dose had been achieved following initial titration, as it was believed that there might be a learning curve for optimal titration associated with use of a new insulin product that would likely have resolved after 16 weeks [22].

3 Results

3.1 Patients Included in the Meta-analysis

A total of 917/4345 (21 %) randomised patients in the seven trials in the IDeg development programme that compared once-daily IDeg with once-daily IGLar were elderly (≥ 65 years of age). Across the trials, the proportion of elderly patients randomised to receive treatment ranged from 6 to 28 % (Table 1). There was a lower proportion of elderly patients in the two T1DM trials than in the five T2DM trials (Table 1). Of the 917 elderly patients randomised to treatment (634 IDeg, 283 IGLar), 61 had T1DM (43 IDeg, 18 IGLar) and 856 had T2DM (591 IDeg, 265 IGLar). The larger number of elderly patients randomised to IDeg treatment reflected the unequal randomisation of 3:1 or 2:1 to IDeg:IGlar in four of the seven trials.

Overall, completion rates were high for both T1DM and T2DM and were similar between the IDeg and IGLar treatment groups (Fig. 1). Patient characteristics generally were similar across treatment groups, both for elderly patients with T1DM and those with T2DM (Table 2). However, compared with the IGLar group, in the IDeg group there was a higher proportion of male patients and a higher proportion of patients with T2DM previously treated with basal insulin \pm OADs. The mean age of elderly patients was similar between groups, ≈ 70 years in both T1DM and T2DM patients. The duration of diabetes was longer in elderly patients with T1DM (≈ 27 years) than those with T2DM (≈ 13 years).

For the overall population in all seven trials, non-inferiority was met with regard to the primary endpoint, change in HbA_{1c} (observed mean baseline and end-of-trial HbA_{1c} for each of the seven trials are provided in Table 1). Mean basal insulin doses in elderly patients were comparable between treatment groups (24.9 U with IDeg and 28.6 U with IGLar in T1DM, and 42.2 U with IDeg and 37.3 U with IGLar in T2DM).

3.2 Hypoglycaemia in Elderly Patients

Hypoglycaemic episodes are summarised descriptively by classification, treatment, and diabetes population over the total treatment period for individual trials and in total in Table 3, in which the proportion of patients experiencing hypoglycaemia and the rate (episodes per PYE) are shown. The total observed proportion of patients with overall confirmed hypoglycaemia during the trials appeared similar between treatment groups both in T1DM [97.7 % (IDeg); 94.1 % (IGlar)] and T2DM [58.7 % (IDeg and IGLar)]. Observed rates of overall confirmed hypoglycaemic episodes were numerically lower in one and higher in the other of the two T1DM trials with IDeg than with IGLar

Fig. 1 Disposition of elderly patients (≥ 65 years of age). *AEs* adverse events, *FAS* full analysis set, *IDeg* insulin degludec, *IGlar* insulin glargine, *SAS* safety analysis set, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus. The *IDeg* flexible arm is excluded from Trials 3770 and 3668. *Two randomised *IDeg* patients from one closed trial site were excluded from the full analysis set before the trial was unmasked

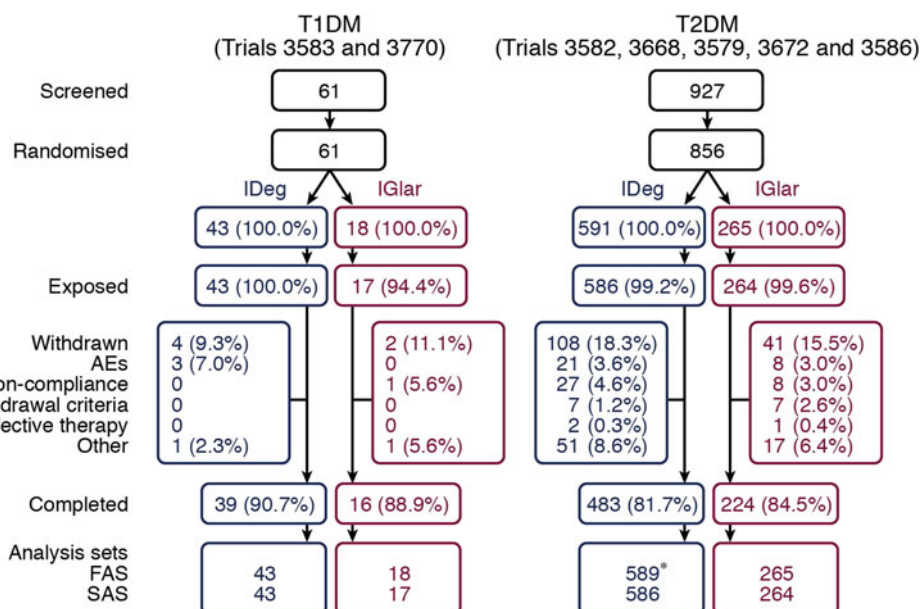


Table 2 Patient characteristics of elderly patients (≥ 65 years of age)

	IDeg	IGlar
<i>T1DM patients</i>		
No. of patients	43	18
Female/male, <i>n</i> (%)	18 (41.9)/25 (58.1)	10 (55.6)/8 (44.4)
Age, years, mean \pm SD	69.6 \pm 3.5	69.9 \pm 3.8
BMI, kg/m ² , mean \pm SD	26.1 \pm 4.1	26.6 \pm 4.6
Duration of diabetes, years, mean \pm SD	28.0 \pm 14.3	26.4 \pm 14.6
<i>T2DM patients</i>		
No. of patients	589	265
Female/male, <i>n</i> (%)	248 (42.1)/341 (57.9)	121 (45.7)/144 (54.3)
Age, years, mean \pm SD	70.1 \pm 3.8	69.9 \pm 3.8
BMI, kg/m ² , mean \pm SD	29.8 \pm 5.2	29.7 \pm 4.8
Duration of diabetes, years, mean \pm SD	13.8 \pm 7.9	13.4 \pm 7.3
Prior antidiabetic therapy, <i>n</i> (%)		
OAD(s) only	368 (62.5)	182 (68.7)
Basal insulin \pm OAD(s)	220 (37.4)	83 (31.3)

Full analysis set

BMI body mass index, *IDeg* insulin degludec, *IGlar* insulin glargine, *OAD(s)* oral antidiabetes drug(s), *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

(overall slightly higher with IDeg). Rates were lower with IDeg in four of the five T2DM trials (overall slightly lower with IDeg).

The total observed proportion of patients with nocturnal confirmed hypoglycaemia was 69.8 % for IDeg and 82.4 % for IGlar in T1DM, and 21.2 % for IDeg and 25.4 % for IGlar in T2DM. Observed rates of nocturnal confirmed hypoglycaemic episodes were again numerically lower in one and higher in the other of the two T1DM trials with IDeg (overall lower with IDeg), and were lower with IDeg in all five T2DM trials (Table 3). Very few episodes of severe hypoglycaemia occurred during the trials: the total proportion of patients with severe hypoglycaemia was

9.3 % (IDeg) and 11.8 % (IGlar) in T1DM, and 2.9 % (IDeg) and 4.2 % (IGlar) in T2DM.

Rates and proportions of patients with overall confirmed, nocturnal confirmed and severe hypoglycaemia during the maintenance period are summarised descriptively in Table 4. During this timeframe, when dose titrations and glycaemic improvements had stabilised, there appeared to be a lower rate of overall confirmed and nocturnal confirmed hypoglycaemia in patients with T1DM in both treatment groups than during the total treatment period. Little difference was observed in severe hypoglycaemia rates, or in the rate of patients with T2DM experiencing overall confirmed or nocturnal confirmed

Table 3 Overall confirmed, nocturnal confirmed and severe hypoglycaemia during the total treatment period in elderly patients, summarised by trial

Trial	Overall confirmed hypoglycaemic episodes per PYE (% patients)		Nocturnal confirmed hypoglycaemic episodes per PYE (% patients)		Severe hypoglycaemic episodes per PYE (% patients)	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
<i>T1DM</i>						
3583	45.73 (96.6)	46.49 (90.0)	3.51 (75.9)	8.28 (70.0)	0.11 (10.3)	0.32 (20.0)
3770	106.04 (100.0)	66.90 (100.0)	14.25 (57.1)	12.53 (100.0)	0.15 (7.1)	0.00 (0.0)
Total	58.06 (97.7)	52.03 (94.1)	5.71 (69.8)	9.43 (82.4)	0.12 (9.3)	0.23 (11.8)
<i>T2DM</i>						
3582	12.50 (86.3)	15.47 (86.2)	1.32 (36.1)	1.51 (44.6)	0.10 (7.3)	0.15 (12.3)
3668	4.35 (50.0)	3.58 (53.7)	0.29 (8.3)	1.02 (26.8)	0.06 (2.8)	0.06 (2.4)
3579	1.68 (50.0)	1.79 (48.6)	0.27 (13.8)	0.37 (14.3)	0.01 (0.5)	0.02 (1.4)
3672	1.06 (31.8)	2.18 (40.8)	0.14 (4.5)	0.50 (12.2)	0.00 (0.0)	0.00 (0.0)
3586	2.90 (41.0)	4.47 (66.7)	0.83 (18.1)	1.07 (28.2)	0.00 (0.0)	0.05 (2.6)
Total	6.19 (58.7)	6.89 (58.7)	0.74 (21.2)	0.91 (25.4)	0.04 (2.9)	0.07 (4.2)

Safety analysis set. Observed rates. The *IDeg* flexible arm is excluded in Trials 3770 and 3668

IDeg insulin degludec, *IGlar* insulin glargine, *PYE* patient-years of exposure, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

hypoglycaemia during the maintenance period as opposed to the total treatment period. The proportion of patients experiencing hypoglycaemia was generally lower in most trials during the maintenance period for both treatment groups; please see Table 4 for more detail.

3.3 Treatment Comparisons of Hypoglycaemia

As previously mentioned, due to the low number of subjects with T1DM (Fig. 1) and few episodes of severe hypoglycaemia in this study, insufficient data were available to perform formal statistical analyses; hence, summary statistics alone are presented for these situations.

Over the total treatment period and maintenance period, respectively, elderly patients with T2DM had a 24 % [ERR (IDeg/IGlar) 0.76 (0.61; 0.95)_{95 % CI}] and 27 % [ERR (IDeg/IGlar) 0.73 (0.56; 0.96)_{95 % CI}] lower estimated rate of overall confirmed hypoglycaemia with IDeg compared with IGlar; both treatment comparisons were statistically significant (Fig. 2a). Estimated rates of nocturnal confirmed hypoglycaemia during the total treatment period and maintenance period were 36 % [ERR (IDeg/IGlar) 0.64 (0.43; 0.95)_{95 % CI}] and 39 % [ERR (IDeg/IGlar) 0.61 (0.37; 1.03)_{95 % CI}] lower with IDeg versus IGlar, respectively; the treatment comparison during the total treatment period, but not the maintenance period, reached statistical significance (Fig. 2b).

As planned in the prespecified meta-analysis, an analysis of the pooled population including elderly patients with T1DM or T2DM was conducted. In this pooled population (T1DM + T2DM), rates of overall confirmed hypoglycaemia were numerically lower with IDeg than IGlar, by 18 %

in the total treatment period and by 21 % in the maintenance period; neither comparison was statistically significant (Fig. 3a). In the pooled T1DM and T2DM population, rates of nocturnal confirmed hypoglycaemia were 35 % lower with IDeg than IGlar in both the total and maintenance periods (this comparison was statistically significant in favour of IDeg for the total treatment period and non-significant during the maintenance period) (Fig. 3b).

4 Discussion

The IDeg phase III development programme studied a representative group of patients with regard to type of disease (T1DM or T2DM), duration of diabetes, previous treatment regimen (insulin naïve or insulin treated), type of insulin regimen studied (basal-only therapy, basal-bolus therapy) and combining insulin with a range of oral anti-hyperglycaemic therapies. More than one-fifth of this large patient population were elderly (≥ 65 years of age) as per FDA guidance [27], and a meta-analysis of the elderly population with T1DM or T2DM was prespecified as part of the overall hypoglycaemia meta-analysis plan.

In the present meta-analysis, patient-level data from more than 900 elderly patients (the majority of whom had T2DM) showed estimated rates of overall confirmed hypoglycaemia that were significantly lower with IDeg than IGlar in T2DM (Fig. 2a). Consistent with these pooled analyses, observed rates of overall confirmed hypoglycaemia were lower with IDeg in four of the five individual T2DM trials (Table 3) during the total treatment period. The proportion of subjects experiencing overall confirmed

Table 4 Overall confirmed, nocturnal confirmed and severe hypoglycaemia during the maintenance period in elderly patients, summarised by trial

Trial	Overall confirmed hypoglycaemic episodes per PYE (% patients)		Nocturnal confirmed hypoglycaemic episodes per PYE (% patients)		Severe hypoglycaemic episodes per PYE (% patients)	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
<i>T1DM</i>						
3583	39.72 (96.2)	43.58 (90.0)	2.95 (69.2)	7.99 (70.0)	0.06 (3.8)	0.47 (20.0)
3770	109.54 (100.0)	65.14 (85.7)	16.73 (42.9)	9.52 (71.4)	0.40 (7.1)	0.00 (0.0)
Total	48.28 (97.5)	47.38 (88.2)	4.64 (60.0)	8.26 (70.6)	0.10 (5.0)	0.39 (11.8)
<i>T2DM</i>						
3582	11.73 (77.1)	13.55 (73.0)	1.24 (24.6)	1.25 (31.7)	0.11 (6.7)	0.10 (4.8)
3668	4.02 (29.4)	4.66 (35.3)	0.15 (2.9)	1.55 (20.6)	0.00 (0.0)	0.00 (0.0)
3579	1.78 (42.2)	2.09 (45.2)	0.34 (13.5)	0.45 (12.9)	0.01 (0.5)	0.03 (1.6)
3672	0.92 (14.6)	2.54 (27.9)	0.00 (0.0)	0.48 (9.3)	0.00 (0.0)	0.00 (0.0)
3586	2.48 (25.0)	3.95 (37.8)	0.69 (10.5)	0.85 (10.8)	0.00 (0.0)	0.00 (0.0)
Total	6.14 (47.5)	6.93 (45.6)	0.73 (15.1)	0.87 (18.0)	0.05 (2.5)	0.05 (1.7)

Safety analysis set. Observed rates. The maintenance period was from week 16 to the end of the trial. The *IDeg* flexible arm is excluded in Trials 3770 and 3668

IDeg insulin degludec, *IGlar* insulin glargine, *PYE* patient-years of exposure, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

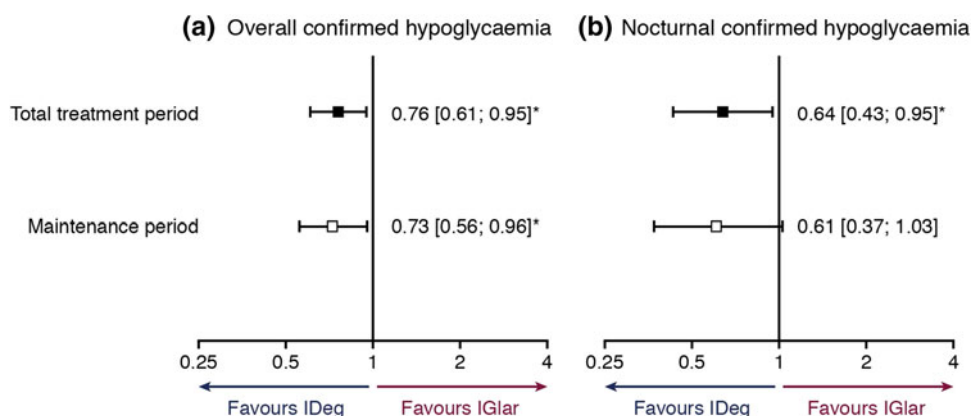


Fig. 2 Estimated rate ratios (IDeg/IGlar) with 95 % confidence intervals in elderly patients ≥ 65 years of age with T2DM for **a** overall confirmed hypoglycaemic episodes, and **b** nocturnal confirmed hypoglycaemic episodes during the total treatment period and maintenance period. *Statistically significant, $p < 0.05$. *IDeg* insulin

degludec, *IGlar* insulin glargine, *T2DM* type 2 diabetes mellitus. Nocturnal confirmed episodes are the subset of overall confirmed hypoglycaemic episodes with onset from 0001 to 0559 hours (both inclusive). The maintenance period was from week 16 to the end of the trials. Full analysis set

hypoglycaemia was lower in three and higher in two of these five trials with *IDeg*. The mean proportion was the same overall for both treatment groups in T2DM, suggesting that while similar proportions of patients in both treatment arms experienced hypoglycaemia, *IDeg* patients tended to experience fewer events, which is likely a result of the ultra-long and stable pharmacokinetic profile and the lower day-to-day variability in glucose-lowering action of *IDeg* [16–18]. Rates of severe hypoglycaemia were low in both treatment groups across trials, for both T1DM and T2DM patients.

Nocturnal confirmed hypoglycaemia was chosen as an endpoint because it better reflects the action of basal insulin

compared with overall confirmed hypoglycaemia, which may be influenced by bolus insulin, meal patterns and the physical activity level during the day. When events of nocturnal confirmed hypoglycaemia were analysed, a greater difference in the relative rate of hypoglycaemia between *IDeg* and *IGlar* in elderly patients with T2DM was observed than for overall confirmed hypoglycaemia (Fig. 2b).

Rates of hypoglycaemia varied and were higher in some trials than others, varying by trial population (T1DM or T2DM, insulin naïve or insulin treated), duration of diabetes and levels of glycaemic control at baseline as well as the treatment regimen (basal only or basal–bolus therapy). In both the *IDeg* and *IGlar* groups, insulin was titrated

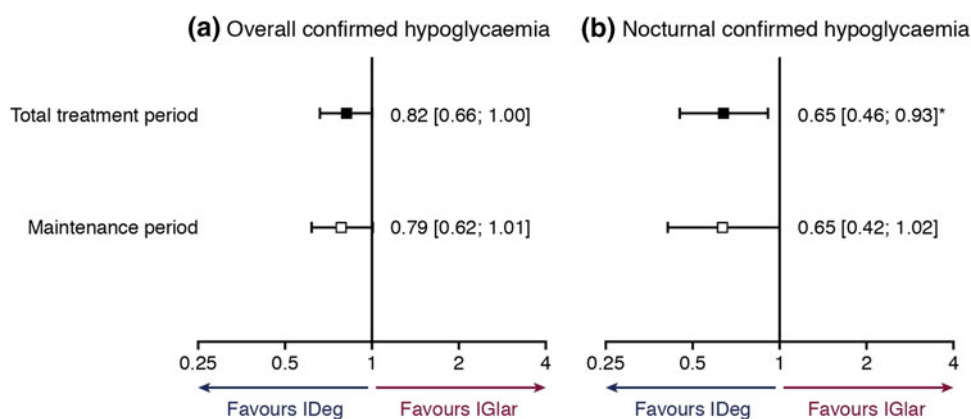


Fig. 3 Estimated rate ratios (IDeg/IGlar) with 95 % confidence intervals in elderly patients ≥ 65 years of age for the pooled population (T1DM + T2DM) for **a** overall confirmed hypoglycaemic episodes, and **b** nocturnal confirmed hypoglycaemic episodes during the total treatment period and maintenance period. *Statistically significant, $p < 0.05$. IDeg insulin degludec, IGlar insulin glargine,

T1DM type 1 diabetes mellitus, T2DM type 2 diabetes mellitus. Nocturnal confirmed episodes are the subset of overall confirmed hypoglycaemic episodes with onset from 0001 to 0559 hours (both inclusive). The maintenance period was from week 16 to the end of the trials. Full analysis set

using standard algorithms to reach similar pre-breakfast glucose targets. The majority of insulin titration and corresponding glycaemic reductions took place during the first 15 weeks of the trials. In the subsequent maintenance period, during which insulin titration and insulin doses were stable, differences in relative rates of both overall and nocturnal hypoglycaemia appeared to be greater than during the total treatment period (Figs. 2 and 3).

Similar to the results in the entire population of both elderly and younger patients reported by Ratner and colleagues [22], the risks of overall confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia over the total treatment period reported in this meta-analysis of elderly patients were significantly lower for IDeg compared with IGlar in T2DM. Hence, the hypoglycaemic benefits with IDeg relative to IGlar demonstrated in this meta-analysis of elderly patients were consistent with that seen in the entire adult patient population.

Limitations of this meta-analysis include the open-label design of the studies, which could potentially bias reporting of hypoglycaemic episodes or insulin dosing. To attempt to reduce reporting bias, all hypoglycaemic episodes either were meter-confirmed with a blood glucose measurement [$PG < 3.1$ mmol/L (56 mg/dL)] or were severe episodes, which by definition required assistance by a third party to treat. The fact that this definition was independent of the presence of symptoms is of particular relevance for elderly patients who may have atypical, less intense, or delayed symptoms of hypoglycaemia [31]. To address potential investigator bias in insulin dosing, the same glycaemic targets and titration algorithms were used for both groups, and a titration committee blinded to treatment identified and discussed deviations from the algorithm with trial investigators

to encourage adherence to the algorithms. Furthermore, although the meta-analysis described in this report was pre-planned, it comprised a subset of data for elderly subjects enrolled in the larger overall phase III trials, and its conclusions could be strengthened further by the collection of additional data from a prospective randomised study designed to demonstrate the superiority of IDeg compared with IGlar with regard to hypoglycaemia risk in the elderly.

Exclusion from the trials of patients who had hypoglycaemic unawareness or more than one severe episode of hypoglycaemia in the last year or who had other serious comorbidities was another limitation, especially because elderly patients with diabetes may be more frequently affected by these conditions than younger patients [9, 32]. However, this criterion for exclusion was applied for safety reasons because these individuals would not be appropriate candidates for intensive titration with insulin to achieve near-normal levels of glycaemic control [< 5 mmol/L (< 90 mg/dL)] [4], as was the goal of treatment in the IDeg phase III trials.

Data from dedicated clinical trials comparing basal insulin treatments in elderly patients are lacking. A meta-analysis of pooled patient-level data from five randomised controlled clinical trials conducted between 1999 and 2002 compared hypoglycaemia with once-daily IGlar versus intermediate-acting once-daily neutral protamine Hagedorn (NPH) in insulin-naïve elderly patients (≥ 65 years) with T2DM [32]. Although the definitions of hypoglycaemia in this meta-analysis of elderly patients differed from those in the present meta-analysis, episode rates appeared lower with IGlar than NPH, both for symptomatic nocturnal hypoglycaemia and severe nocturnal hypoglycaemia; however, treatment differences did not reach statistical significance [32].

5 Conclusion

Consistent with the results of the meta-analysis of the overall patient population [22], this meta-analysis of IDeg phase III trials demonstrated that elderly patients also experience lower rates of hypoglycaemic episodes with IDeg compared with IGLar, particularly during the night. The reduced risk of hypoglycaemia found with IDeg relative to IGLar in this analysis should be taken into account when considering insulin treatment for elderly patients with diabetes.

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